ECT: Its Brain Enabling Effects

A Review of Electroconvulsive Therapy–Induced Structural Brain Plasticity

Filip Bouckaert, MD, Pascal Sienaert, MD, PhD,* Jasmien Obbels, MSc,* Annemieke Dols, MD, PhD,† Mathieu Vandenbulcke, MD, PhD,* Max Stek, MD, PhD,† and Tom Bolwig, MD, PhD‡*

Background: Since the past 2 decades, new evidence for brain plasticity has caused a shift in both preclinical and clinical ECT research from falsifying the "brain damage hypothesis" toward exploring ECT's enabling brain (neuro)plasticity effects.

Methods: By reviewing the available animal and human literature, we examined the theory that seizure-induced structural changes are crucial for the therapeutic efficacy of ECT.

Results: Both animal and human studies suggest electroconvulsive stimulation/electroconvulsive therapy (ECT)-related neuroplasticity (neurogenesis, synaptogenesis, angiogenesis, or gliogenesis).

Conclusion: It remains unclear whether structural changes might explain the therapeutic efficacy and/or be related to the (transient) learning and memory impairment after ECT. Methods to assess in vivo brain plasticity of patients treated with ECT will be of particular importance for future longitudinal studies to give support to the currently available correlational data.

Key Words: electroconvulsive therapy, neuroplasticity, neurogenesis, angiogenesis, synaptogenesis, gliogenesis, hippocampus, BDNF, magnetic resonance imaging

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Concerned professionals and critics of electroconvulsive therapy (ECT) have argued that ECT is causing brain damage.[1–4] Since the past 2 decades, new evidence for brain plasticity[5] has caused a shift in both preclinical and clinical ECT research from falsifying the "brain damage hypothesis"[6–10] toward exploring ECT's enabling brain (neuro)plasticity effects.

Neuroplasticity refers to the brain's ability to reorganize itself. This is achieved by synaptic structural remodeling through the formation, organization, and maintenance of neurite components of synapses (synaptogenesis) as well as by the generation of new neurons (neurogenesis)[11] in the subventricular zone[12] and the subgranular layer of the dentate gyrus in the hippocampus.[13] Although there is limited cortical synaptogenesis and slower turnover of new hippocampal neurons beyond adolescence, these are nevertheless, stimulated by antidepressant therapy and hampered in depressive states.[11] Stress reduces adult hippocampal neurogenesis,[14,15] produces dendritic atrophy,[16] and leads to decreased hippocampal volume,[17] possibly secondary to a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and hypercortisolemia. Depression itself has also been reported to reduce hippocampal volume.[18–22] Hypothalamic-pituitary-adrenal feedback dysregulation might be explained by marked changes in the function of the amygdala (increased), hippocampus (decreased), and the prefrontal cortex (decreased).[11,23]

According to the neurotrophin hypothesis,[5,24] aberrant neurogenesis is caused by a (stress-induced) lower expression of brain-derived neurotrophic factor (BDNF), but antidepressant therapy restores most aspects of this HPA dysregulation.[11] Cell proliferation and increase in newborn neurons increases hippocampal inhibitory control over the HPA-axis activity after stress.[25–27] Although there is strong evidence from preclinical and clinical studies to support a neurotrophin hypothesis of depression, there are also limitations, the main caveat being that decreased neurogenesis does not always induce depressive behaviors.[28–30] Low serum levels of BDNF are a state abnormality that is evident during depression and normalizes during remission in patients treated with antidepressant.[31–34] However, a recent meta-analysis showed that low BDNF levels in depressed patients are probably less robust, possibly due to a large amount of unexplained between-study heterogeneity in outcomes, underpowered study designs, and publication bias of previous meta-analyses.[34] Increases in serum levels of BDNF during antidepressant treatment seem to be confined to some antidepressants and do not parallel clinical characteristics, such as the severity of depressive symptoms.[31]

Research has been particularly focused on the question whether stress-induced changes in structures like hippocampus, amygdala, and prefrontal cortex can be reversed by antidepressive therapies, such as electroconvulsive stimulation (ECS; an animal model for ECT) and ECT, and whether this correlates with clinical improvement. Here, we present a review of the literature examining the combined anatomical-ictal theory,[35] enouncing that seizure-induced effects in the limbic system are crucial for the therapeutic efficacy of ECT.

MATERIALS AND METHODS

We conducted a PubMed literature search from the inception of the database until December 2013 using the following search terms: ECT combined with (All Fields and MeSH Terms) neuronal plasticity or neurogenesis or angiogenesis or synaptogenesis or gliogenesis or hippocampus or magnetic resonance imaging (MRI) or BDNF or magnetic resonance spectroscopy.

Our search included all research papers from a neuroplasticity perspective along the search strategy aforementioned on depression and depression models in rodents, nonhuman primates and humans. Data published as posters were not included. As the detection of neurogenesis requires evidence that cell division has taken place and that the proliferating cells differentiate and mature into neurons,[36] papers were included when based on this evidence. As BDNF surpasses all other neurotrophins in its role in regulating synaptic plasticity, we focused on this neurotrophin. We excluded papers on magnetic seizure therapy and transcranial magnetic stimulation, papers describing

From the *University Psychiatric Center KU Leuven, Leuven, Belgium; †VUmc Amsterdam/GGZinGeest, Amsterdam, the Netherlands and ‡Institute of Neuropsychiatry, Copenhagen, Denmark.

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Reprints: Filip Bouckaert, MD, University Psychiatric Center KU Leuven, Leuvensesteenweg 517, 3070 Kortenberg (e-mail: filip.bouckaert@uc-kortenberg.be).

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TABLE 1. Selected Publications Showing the Effect of ECS on Neurogenesis and Synaptogenesis

Author, Year	Species/N	Used Technique to Assess Sprouting and Cell Proliferation	Summary of Findings
Jorgensen and Bolwig, 1979	Rats N=30	Quantitative immunoelectrophoresis of rat brain synaptic proteins	ECS results in synaptic proteins, suggesting hippocampal synaptogenesis; sustained increase in the neuronal cell adhesion molecule (N-CAM), which is involved in synaptogenesis
Bolwig et al, 1980	Rats N=36	Crossed immunoelectrophoresis	ECS results in synaptic proteins, suggesting hippocampal synaptogenesis
Vaidya et al, 1999	Mice N=29 Rats N=16	Timm staining, cell counting, and Nadler silver staining	Repeated (5–10 daily treatments), but not a single ECS significantly increases hippocampal granule cell; sprouting (maximum at 12 days after last ECS). Effect still observed up to 6 months after the last ECS. Increased expression of brain-derived neurotrophic factor is necessary but not sufficient for the induction on this sprouting.
Madhav et al, 2000	Rats N=8 (4 sham and 4 ECS)	5-HT immunocytochemistry	Repeated ECS (5 ECSs over 10 days) promotes mossy fiber sprouting and the sprouting of serotonergic axons in the lesioned rat hippocampus.
Madsen et al, 2000	Rats N=63	BrdU followed by double staining with a neuron-specific marker	A single ECS significantly increased the number of newborn cells in the dentate gyrus, which survived for at least 3 months. A series of seizures further increased neurogenesis, indicating a dose-dependent mechanism.
Malberg et al, 2000	Rats N=32	BrdU	BrdU-positive cells significantly increased in the animals treated with chronic ECS, suggesting ECS increases neurogenesis.
Scott et al, 2000	Rats N=13 (6 sham; 7 ECS)	BrdU and NeuN quantification	One month after 8 ECS seizures, ECS-treated rats had approximately twice as many BrdU-positive cells as sham-treated controls in the dentate gyrus.
Hellsten et al, 2002	Rats N=36	BrdU and NeuN	ECS can increase hippocampal neurogenesis even in the presence of elevated levels of glucocorticoids, known to suppress hippocampal neurogenesis.
Segi-Nishida et al, 2008	Rats N=12 (6 sham; 6 ECS)	BrdU and triple immunostaining to characterize the phenotype of BrdU-labeled cells	At an early mitotic phase, ECS increases the proliferation of quiescent progenitors and then at a later phase increases the proliferation of amplifying progenitors in the subgranular zone of the dentate gyrus.
Chen et al, 2009	Rats N=20 (9 sham; 11 ECS)	BrdU	Neurogenesis, synaptogenesis, and remodeling of synapses were demonstrated; a highly significant increase in the number of synapses and an increased synaptic density in the CA1 area of the hippocampus in rats given repeated ECS were shown.
Ito et al, 2010	Rats N=24	BrdU	Application of a single ECS and 10 ECSs increased cell proliferation in the SGZ, whereas 20 ECSs did not produce a difference in cell proliferation compared to the sham group. Ten times ECS induced a significant increase in cell proliferation by 1.3-fold compared to a single ECS group.
Zhao et al, 2012	Rats N=12	Hippocampal injection of the GFP retrovirus	Administration of ECS promotes the maturation of dendritic spines in newborn cells and increases spine density in mature cells, suggesting that newborn granule cells form stronger synaptic connections within the dentate circuitry.

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TABLE 1. *(Continued)*

Author, Year	Species/N	Used Technique to Assess Sprouting and Cell Proliferation	Summary of Findings
Nakamura et al, 2013	Rats N=12	BrdU, NeuN, S-100b	The amount of cell proliferation in the hippocampus 3 days after a series of 10 repeated ECS sessions increased twice as much as the sham-treated group.
Weber et al, 2013	Mice 5 ECS and 5 sham groups. N = 3–8 per group.	Transgenic fate mapping; type 1 cells and their progeny are selectively labeled with the reporter protein b-galactosidase	ECS exerts (over 3 months) a powerful proneurogenic effect in the dentate gyrus by stimulating asymmetric proliferation of type 1 cells, the progeny of which develops into granule neurons.

BrdU, bromodeoxyuridine, a thymidine analog that labels dividing cells in S-phase, is a marker of dividing cells; NeuN is a cell-specific biomarker; S-100b is a glial cell marker ; GFP retrovirus, green fluorescent protein retrovirus, was used to label newborn granule cells and to examine whether their integration is regulated by ECS.

genetic expressions after ECS/ECT, and papers examining the neurophysiology and underlying signaling and binding mechanisms or pathways, as these were beyond the scope of this review. References of all relevant articles were screened for additional papers.

RESULTS

We included 11 articles on neuroplasticity, 24 on neurogenesis, 6 on angiogenesis, 3 on synaptogenesis, 5 on gliogenesis, 10 on MRI and hippocampal changes, 25 on BDNF (of which 11 were in humans), 6 on magnetic resonance spectroscopy.

Twenty-seven studies (some of which overlap across categories) have examined neurogenesis, synaptogenesis, angiogenesis, or gliogenesis of ECS in animals (rodents, n = 25; and nonhuman primates, n = 2). Neuroplasticity effects of ECT in humans were described in 4 recent MRI studies, with a total of 37 subjects.

Neuroplasticity of ECS in Animals

Chronic administration of antidepressants increases BDNF expression in the hippocampus of animal models.[37,38] Electroconvulsive stimulation in animals has also shown an increase in serum BDNF,[39–41] although this has not always been confirmed.[42] Up-regulation of BDNF expression suggests a role for synaptic plasticity and alterations of neuronal structure in the actions of long-term ECS.[43] Expression of BDNF predominantly occurs in hippocampus, prefrontal cortex area, striatum, and occipital cortex,[39,40] although some authors report different results.[38,44] Consistent with the effect of ECS on growth factors, preclinical studies have shown that ECS leads to increased neurogenesis, synaptogenesis, angiogenesis, and glial proliferation in the hippocampus. Only recently, the first evidence that ECS is changing neuroplasticity outside the hippocampus (frontal brain area,[45] amygdala[46,47]) was published. Tables 1 to 3 give an overview of selected publications showing the effect of ECS on neurogenesis and synaptogenesis,[7,48–59] angiogenesis,[60–66] and gliogenesis.[67–73]

Neuroplasticity of ECS in Nonhuman Primates

Perera et al[8] have shown in 6 adult *Macaca radiata* monkeys that ECS robustly increased precursor cell proliferation in the subgranular zone of the dentate gyrus. Most of these precursors differentiated into neurons or endothelial cells, whereas a few matured into glial cells. The ECS interventions were not accompanied by increased hippocampal cell death or injury, which was confirmed by another nonhuman primate study (8 *Macaca mulatta* monkeys) showing no change in the number of neurons or glia in the hippocampal pyramidal cell layer (CA1-CA3) and frontal cortex, likely areas for neuronal damage.[10]

Neuroplasticity of ECT in Humans

BDNF and ECT

Brain-derived neurotrophic factor surpasses all other neurotrophins in its role in regulating synaptic plasticity and has been investigated in ECT by several research groups. Table 4 shows the conflicting associations between changes in serum or plasma BDNF levels and the clinical improvements after ECT in patients with treatment-resistant depression.[74–84]

Structural Imaging

Differing results have been reported as to the effect of ECT on brain structure. Few studies have compared structural brain imaging (computed tomography and MRI) findings before and after an ECT course. Studies conducted at a single time after ECT (and thus suffering from severe methodological problems) showed a temporary increase of T1 relaxation[85,86] or T2 relaxation[87] time, suggesting temporary breakdown of the blood-brain barrier during ECT. None of the MRI studies[85,88–92] could provide evidence of persistent structural changes after a course of ECT. Kunigiri et al[93] showed no increase in T2 relaxation time (corresponding to water content) in the hippocampus after ECT, suggesting that hippocampal edema does not result from ECT.

Nordanskog et al[94,95] investigated 12 patients with depression and ongoing antidepressive pharmacological treatment with clinical ratings and 3-T magnetic resonance imaging within 1 week before and after the ECT series in a prospective study. They found a significant volume increase in the left hippocampus as well as in the right hippocampus after ECT (mean volume increase of right hippocampus, 4.3%; and mean volume increase of left hippocampus, 5.1%). There was no evidence of edema in the hippocampus on T2-weighted fluid-attenuated inversion recovery images.[94] However, in a follow-up study after 6 months,[95] this volume increase returned to baseline. The authors concluded that the immediate increase in hippocampal volume after ECT was reversible and not related to clinical or cognitive outcome and suggested that the volume decrease could represent a trait-dependent vulnerability of the patients to depression, taking place before recurrence of the disease.

TABLE 2. Selected Publications Showing the Effect of ECS on Angiogenesis

Author, Year	Species/N	Used Marker/Technique	Summary of Findings
Hellsten et al, 2004	Rats N=23 (6 control; 17 ECS)	BrdU	Endothelial cell and neural precursor proliferation in the dentate gyrus occurred in concert.
Hellsten et al, 2005	Rats N=12 (6 sham; 6 ECS)	Total number of endothelial cells and vessel length estimated using design based stereological analysis methods. Endothelial cell proliferation was assessed using BrdU	Increase in endothelial cell proliferation leading to a 30% increase in the total number of endothelial cells in the ML of the DG with or without preoxygenation precluding hypoxia was seen. The increase in cell number resulted in a 16% increase in vessel length.
Newton et al, 2006	Rats N=28 (14 sham; 14 ECS)	A combination of vascular density quantification, angiogenic gene expression analysis, and immunohistochemistry	A 6% increase in vascular density in the dentate gyrus. Another hippocampal region, the stratum lacunosum moleculare exhibited a robust 20%–30% increase in vascular density.
Jansson et al, 2006	Rats N=38 (14 control; 24 ECS)	BrdU and the endothelial cell marker rat endothelial cell antigen-1	A correlating pattern of increases in neuronal activation and increased endothelial cell proliferation in different hypothalamic areas was found.
Ekstrand et al, 2008	Rats N=22	BrdU	Despite common factors regulating neurogenesis and angiogenesis, ECS-induced proliferation of neuronal precursors can take place even if the angiogenic response is blunted by corticosterone.
Warner-Schmidt et al, 2008	Rats N=8 (4 control; 4 IRR)	BrdU; a single 10-Gy IRR dose or repeated 5-Gy dose	Disruption of neurogenesis in rat hippocampus produced by low doses of irradiation was reversed by ECS. Vascular endothelial growth factor (VEGF) was an essential mediator of this effect.

DG, dentate gyrus; IRR, (low dose) irradiation; ML, molecular layer.

Tendolkar et al[96] investigated the effect of bitemporal ECT on hippocampus and amygdala volume in 15 antidepressant-free patients with treatment-refractory depression. Analysis of normalized volumetric data before and after ECT revealed a significant volume increase of both hippocampus and amygdala without evidence for a change in global brain volume. There was no correlation with the clinical response.

Dukart et al[97] carried out a study with drug-responsive patients receiving no ECT (n = 24) and drug-resistant patients receiving right unilateral ECT (n = 10). The effect of ECT on

TABLE 3. Selected Publications Showing the Effect of ECS on Gliogenesis

Author, Year	Species/N	Used Marker/Technique	Summary of Findings
Wennstrom et al, 2003	Rats N=18 (6 control; 12 ECS)	BrdU and specific cell type markers such as chondroitin sulfate proteoglycan (NG2)	ECS can induce a strong proliferation of glial progenitor cells in the adult rat hippocampus.
Wennstrom et al, 2004	Rats N=12 (6 control; 6 ECS)	BrdU	ECS significantly increased the number of NG2+ glial cells (also considered as a neurogenesis precursors) and mature oligodendrocytes in the adult rat amygdala.
Wennstrom et al, 2006	Rats N=47 (24 sham; 23 ECS)	BrdU and analyzed for colabeling with the glial cell markers	ECS is able to counteract the glucocorticoid-induced inhibition of NG2+ cell proliferation and restore the gliogenesis rate to baseline levels.
Jansson et al, 2009	Rats N=20	The expression of 2 different markers for activated microglia and 1 marker for activated astrocytes (nestin) were analyzed in 3 different double immunofluorescence stainings	ECS induced transient glial cell activation in prefrontal cortex, hippocampus, amygdala, hypothalamus, piriform cortex, and entorhinal cortex regardless of the stimulus parameter used.
Kaae et al, 2012	Rats N=32 (16 sham; 16 ECS)	Optical fractionator with varying sampling fractions was used to count neurons or glial cells	ECS increased the number of glial cells in hilus significantly.

TABLE 4. Electroconvulsive Therapy Human Studies and BDNF

Author, Year	N	Sex (F/M)	Mean Age	Electrode Position	Medication	Results
Bocchio-Chiavetto et al, 2006	23	16/7	53	BL	Anti-D	Increase of serum BDNF 1 day and 1 month after last ECT and in a patient subgroup that had low baseline BDNF levels.
						No correlation between BDNF levels and depressive symptoms (MADRS).
Marano et al, 2007	15	4/11	50	BF/BT	Anti-D	Increase of plasma BDNF after the fourth ECT compared to 1 day before ECT.
						Change accompanied by significant decrease in HAM-D score in 13 subjects.
Okamoto et al, 2008	18	9/9	60.6	BL	Anti-D	Responders showed increase of serum BDNF 5 weeks after first ECT; nonresponders (n = 6) did not show increased serum BDNF.
Fernandes et al, 2009	15	10/5	52.7	UL	Anti-D; anti-P	No changes in serum BDNF between baseline and day of last ECT.
Gronli et al, 2009	10	NA	NA	UL	Anti-D and or PT	No changes in serum BDNF between baseline, after the fourth ECT and eighth ECT.
Piccinni et al, 2009	18	9/9	44.9	BL	Anti-D; mood stabilizers	Increase of plasma BDNF 1 week after last ECT although only in remitted patients with increased baseline plasma BDNF; parallel with clinical response.
Hu et al, 2010	28	23/5	41	BF	No anti-D	Increase of serum BDNF 2 weeks after completion of ECT compared to baseline.
						Increasing rate of serum BDNF correlating with decreasing rate of HAM-D.
Gedge et al, 2012	11	7/4	46.5	NS	Anti-D; benzo; anti-P	No difference between pretreatment and posttreatment serum BDNF levels (7 days before ECT and 7 days after treatment completion)
Lin et al, 2013	55	44/11	46.5	BF	No psychotropics	No change of plasma BDNF after last ECT and no correlation with clinical response
Stelzhammer et al, 2013	12	NS	52. 6	UL but only 2.5× above ST	Anti-D after first 2 weeks	Decreased serum BDNF levels after acute ECT.
						Patients received only ECT treatments over the first 2 weeks and a combination of ECT and antidepressant drugs (AD) over the subsequent 2 weeks. Sera were taken 6 hours after ECT.
Haghighi et al, 2013	40	30/10	31.4	BF	Citalopram	Comparison of group taking citalopram only and group taking citalopram and additional 12 ECT sessions.
						101% increase of plasma BDNF in citalopram and ECT group, without relation to decrease in symptom severity.

Anti-D, antidepressants; anti-P, antipsychotics; benzo, benzodiazepines; BF, bifrontal electrode position; BL, bilateral electrode position; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; N, number of subjects; NS, not specified; ST, seizure threshold; UL, unilateral electrode position.

brain anatomy was monitored using voxel-based morphometry on magnetic resonance brain data at entry and at 3 months. Electroconvulsive therapy was correlated with regional increases in local gray matter volume (GMV) only in the right hemisphere, and significantly higher GMV was demonstrated in the subgenual cortex and hippocampal complex (hippocampus, amygdala, and anterior temporal pole), paralleled by prefrontal cortex GMV decreases in the ECT group compared with patients with no ECT. A significantly higher GMV in hippocampal complex was also seen compared to the control group (n = 21). Changes in GMV in the subgenual cortex and the hippocampal complex were also significant predictors of improved depression scores after ECT.

Magnetic Resonance Spectroscopic Imaging

Magnetic resonance spectroscopic imaging studies are considerably more sensitive than structural imaging in assessing pathologic changes in the brain even if morphologic changes are absent.[98] It allows a view of brain chemical activity. *N*-acetylaspartate (NAA), an amino acid exclusively located in neurons, has been demonstrated to be a sensitive marker of neural function. In a sample of 17 patients treated with ECT, Ende et al[99] found no immediate changes in the NAA signal, corroborating that ECT does not lead to immediate neuronal loss or dysfunction. A significant increase in signals from choline (Ch)-containing compounds in these 17 patients was seen during and immediately after a complete course of ECT. Patients'

pre-ECT Ch signals were low compared with those of healthy subjects. An increased Ch signal might reflect an ECT-induced increased membrane turnover, possibly owing to mossy fiber sprouting. These findings have been replicated in both human[98,100] and animal studies.[101–103]

DISCUSSION

Most results presented in the animal studies are in line with the neurogenesis hypothesis and support the idea of an important influence of ECS on neuroplasticity. However, the animal data are based on unchallenged animals or they apply to experimental models useful only in studies of stress.[35] It is therefore difficult to ascertain if alterations in hippocampal neurogenesis are due to stress, anxiety, depression, or a combination. Only the nonhuman primates studies used an untreated control group (next to a treatment and sham group) to show increased cell proliferation after ECS.

Similar to studies with antidepressant treatment, animal studies have shown an increased number of neurons in the hippocampus after ECS, and inhibitory effects of stress on neuroplasticity have been found to be diminished by ECS.[50] Hippocampal neurogenesis seems to be necessary for antidepressive effects,[104,105] although this has been and still is a matter of debate.[29,106] A decrease in neurogenesis does not seem to be causative for depression.[30]

Electroconvulsive stimulation is clearly a more potent stimulator of neuroplasticity than antidepressants[55] and increases cell proliferation by 2.5- to 4-fold compared with approximately 1.5-fold for antidepressants.[107] Another example of the more potent mechanism of ECS is shown by the increase in proliferation of neural stem cells at an early mitotic phase followed by increases of neural progenitor cells at a later phase in the subgranular zone of the hippocampus.[65] Chronic administration of fluoxetine only increases proliferation of neural progenitor cells in the hippocampus without affecting neural stem cell proliferation.[108] Although limited by data in mice that did not show a depressivelike phenotype before ECS, Weber et al[58] (2013) provided the definitive link between ECS-induced type-1 cell proliferation and the generation of newborn neurons. Normalizing or enhancing hippocampal neurogenesis during depression could restore the hippocampus as central regulator of HPA system activity.[27,109]

In animal models, it has been suggested that increased expression of BDNF is necessary but not sufficient for the induction of mossy fiber sprouting.[7] However, ECS-induced mossy fiber sprouting and BDNF expression are attenuated by ketamine pretreatment,[110] whereas cell proliferation seems to be still present.[111]

The human data are based on relatively few patient groups.

The inconsistencies in the available literature on the topic of ECT and BDNF reflects heterogeneity among the included patients in diagnosis and clinical features (polarity of illness, presence of psychotic features, and history of treatment resistance), and a heterogeneity in the used methodology (electrode placement, concomitant psychotropic drug treatment), measurement in peripheral blood (serum or plasma), timing of blood sampling, technique to assay BDNF levels, use of different enzyme-linked immunosorbent assay kit).[79,112,113] Given the conflicting results, future studies on serum levels of BDNF should also correct for the time of blood withdrawal, storage time and temperature, urbanicity, age, sex, smoking status, and food and alcohol intake.[114] Whereas ECT may increase BDNF levels, it remains unclear as to when this increase occurs. The time point at which posttreatment BDNF levels are measured has not been consistent throughout the studies (during treatment, the day after the last ECT, 1 week after the end of ECT, or 1 month after the end of ECT). For the time being, it is too early to conclude that the effect of ECT on BDNF is central to the efficacy of ECT in the treatment of major depressive disorder. It is also not clear whether BDNF and other growth factors are markers or rather mechanisms of illness improvement.[78]

Three recent longitudinal MRI studies have demonstrated increases in hippocampal volume after ECT,[94–97] with one reporting a return to baseline at a later time point.[95] There is some evidence suggesting that edema is unlikely to be the primary cause of these volume changes, opening up the possibility of a neuroplasticity-based hypothesis.[93,94]

The hippocampal volume increase seen in these longitudinal MRI studies after ECT[94–97] could be related to a restoration of cell number or neuropil, as antidepressants reverse dendritic shrinkage and improve cell survival, activating the antiapoptotic protein Bcl-2 and BDNF expression.[115,116] Interestingly, ECT up-regulates the antiapoptotic gene BCL2 in the dentate regions where neurogenesis occurs.[117] However, as the volume increase was seen 1 week after treatment, it may well reflect short-term structural plasticity mediated by increases in progenitor proliferation.[118]

Nordgren et al[119] hypothesized that ECT causes transient down-regulation of key molecules needed to stabilize synaptic structures and to prevent calcium influx, and a simultaneous increase in neurotrophic factors, thus providing a short time window of increased structural synaptic plasticity. Their findings indicate that the window of plasticity with increased neuromodulation is followed by a later phase during which the synaptic network is stabilized in a new, slightly altered configuration. Both effect and adverse effects of ECT may thus be caused by structural synaptic rearrangements, as already suggested 2 decades ago.[120]

Future research should develop radiopharmaceutical molecules tagged with positron-emitting isotopes enabling in vivo neuroimaging of neuroplasticity[121] to study cell proliferation, cell connectivity, and functional integration into brain circuits before, during, and after ECT.

We need to continue investigating whether seizure-induced structural changes are crucial for the therapeutic efficacy of ECT, have impact on cognitive changes, or should rather be considered as an epiphenomenon.

CONCLUSION

It remains unclear whether structural changes might explain the therapeutic efficacy and/or be related to the (transient) learning and memory impairment after ECT. Methods to assess in vivo brain plasticity of patients treated with ECT and its correlations with treatment outcome will be of particular importance for future longitudinal studies to give support to the currently available correlational data.

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